

AMENDMENTS TO THE SPECIFICATION

In the paragraph starting on page 3, line 7, please amend the specification as follows:

NMR microcoils are known to those skilled in the art and are shown, for example, in US patent 5,654,636 to Sweedler et al., and in US patent 5,684,401 to Peck et al., and in US patent 6,097,188 to Sweedler et al., all three of which patents are incorporated herein by reference in their entireties for all purposes. A solenoid microcoil detection cell formed from a fused silica capillary wrapped with copper wire has been used for static measurements of sucrose, arginine and other simple compounds. Wu et al. (1994a), J. Am. Chem. Soc. 116:7929-7930; Olson et al. (1995), Science 270:1967-1970, Peck (1995) J. Magn. Reson. 108(B) 114-124. Coil diameter has been further reduced by the use of conventional micro-electronic techniques in which planar gold or aluminum R.F. coils having a diameter ranging from 10-200 μm were etched in silicon dioxide using standard photolithography. -Peck 1994 IEEE Trans Biomed Eng 41(7) 706-709, Stocker 1997 IEEE Trans Biomed Eng 44(11) 1122-1127, Magin 1997 IEEE Spectrum 34 51-61, which are also incorporated herein by reference in its entirety for all purposes. In Stocker et al. a microcoil was fabricated on a gallium arsenide substrate with an inner diameter of 60um, an outer diameter of 200um, trace width of 10um, trace spacing of 10um, and trace height of 3um. At 5.9T (250MHz) in 1H-NMR microspectroscopy experiments using a spectral width of 1kHz, 4096 sampled data points, and a recovery delay of 1s, a SNR of 25 (per acquisition) and a spectral linewidth of less than 2Hz were obtained from a sample of water.

In the paragraph starting on page 3, line 21, please amend the specification follows:

Miniature total analysis systems (μ -TAS) are discussed in Integrating Microfluidic Systems And NMR Spectroscopy - Preliminary Results, Trumbull et al, Solid-State Sensor and

Actuator Workshop, pp. 101-05 (1998), Magin 1997 IEEE Spectrum 34 51-61, and Trumbull 2000 47(1) 1-6 incorporated herein by reference in its entirety for all purposes. These groups constructed chip-based capillary electrophoresis (CE) devices equipped with an integrated planar radio frequency detector coil used for nuclear magnetic resonance spectroscopy (NMR). Separations were accomplished in the devices, but satisfactory NMR spectra could only be obtained from samples of high concentration. Two prototype CE-NMR devices are presented that represent complete microanalytical instruments. Further, "The first system, Trident, was designed to be a proof-of-concept fluidic-NMR device to gauge the effectiveness of integrated, single-turn planar NMR coils. The channel network was formed by solvent bonding a photopatterned polyimide coating (on a glass slide) with a cover-glass coated with a thin layer of polyimide. Holes were previously drilled ultrasonically in the glass slide to provide access. A lift-off process was used to create a 1 mm diameter, single-turn coil on the outer surface of the cover glass. The metal was formed from 3 evaporated layers: Cr/Cu/Cr with respective thicknesses of 150, 9700, and 150 angstroms for improved susceptibility matching. The resistance of the coil, pad to pad, was measured to be 5.9Ω . Acrylic wells were then placed over the drilled holes and bonded with epoxy. The second device type created, SpinCollector shown in Fig. 1 blowups, was made from etched glass channels using methods developed from (D.J. Harrison and N. Chiem, "Immunoassay Flow Systems On-Chip," TRF, pp. 5-8, 1996). Annealed Pyrex glass wafers (1 mm thick) were etched in HF and HNO₃ to a depth of 20 μm through a Cr/Au mask. Access holes were drilled ultrasonically and the mask was stripped. The wafers were then cleaned in a 1% HF bath for 1 minute with ultrasonic agitation to remove any loose glass particles. After thorough cleaning, the wafers were thermally bonded to unprocessed pieces forming closed channels. A 5 mm diameter, single-turn coil was then formed through lift-off on the undrilled cover-glass slide over the disk-shaped reservoir, and glass wells were attached using epoxy. The Trumbull et al. device integrated multiple chemical processing steps and the means of analyzing their results on the same miniaturized system. Specifically, Trumbull et al. coupled chip-based capillary electrophoresis (CE) with nuclear magnetic resonance spectroscopy (NMR) in a μ -TAS system.

In the paragraph starting on page 4, line 20, please amend the specification follows:

Capillary scale systems also are shown in United States patent No. 6,194,900, the entire disclosure of which is incorporated herein by reference for all purposes. [[--]] In such systems, a capillary-based analyte extraction chamber is connected to an NMR flow site, such as by being positioned as an operation site along a capillary channel extending to the NMR flow cell.

In the paragraph starting on page 5, line 3, please amend the specification follows:

Small volume flow probes are shown, for example, by Haner et al. in *Small Volume Flow Probe for Automated Direct-Injection NMR Analysis: Design and Performance*, J. Magn. Reson., 143, 69-78 (2000), the entire disclosures of which is incorporated herein by reference for all purposes. Specifically, Haner et al show a tubeless NMR probe employing an enlarged sample chamber or flowcell. In Haner et al., a 600 MHz, indirect detection NMR flow probe with a 120 μ L active volume is evaluated in two configurations: first as a stand-alone small volume probe for the analysis of static nonflowing solutions, and second as a component in an integrated liquids-handling system used for high-throughput NMR analysis. Key advantages of the flowprobe include high molar sensitivity, ease of use in an automation setup, and superior reproducibility of magnetic field homogeneity which enables the practical implementation of 1D T2-edited analysis of protein-ligand interactions. Microcoil-based micro-NMR spectroscopy is disclosed in United States patent No. 5,654,636, United States patent No. 5,684,401, and United States patent No. 6,097,188, the entire disclosures of all of which are incorporated herein by reference for all purposes. Sample amounts can now range as small as several hundred microliters for conventional flowprobes to smaller than 1 μ L for microcoil-based capillary-scale flowprobes. Acquisition times typically range from minutes to hours. The most expensive and technologically limiting component of the NMR system is the superconducting magnet. Although significant financial and technical investment has been made in the development of elaborate mechanical (robotic-controlled) sample changers and, more recently, automated flow

injection systems for repetitive and continuous sample throughput, the magnet remains today a dedicated component in which only sequential, one-at-a-time analysis of samples is carried out.

In the second paragraph on page 24, please amend the specification follows:

Li et al. (Li 1999 Anal. Chem. 71 4815-4820) describes a 4-coil assembly illustrative of certain aspects of the present disclosure. The solenoidal microcoils are mounted on horizontal (transverse to B_0) capillaries with a 90 degree rotation (x, y) and 5 mm vertical spacing between adjacent coils. Additional details of basic construction are known generally, as shown in the Li et al reference mentioned above. ~~and incorporated herein by reference for all purpose~~ The Li et al. microcoils were fabricated using techniques previously described in detail (Olson et al., Anal. Chem. 70, pp.257A-264A, 1998, and Webb et al., J. Magn. Reson. B 113, pp. 83-87, 1996). A four-coil system was constructed for operation in a 250 MHz wide-bore (89mm) magnet; a two-coil system could be accommodated in either a narrow-bore (54mm) or wide-bore 500 MHz magnet. For the four-coil system, each coil was fabricated identically using 17 turns of 50 μ m diameter copper wire with a 6 μ m thick polyurethane coating (California Fine Wire, Grover Beach, CA) wrapped around a 355 μ m outer diameter, 180 μ m inner diameter polyimide-coated fused silica capillary (Polymicro Technologies, Phoenix, AZ), giving an observe volume (V_{obs}) of 28 nL. The microcoils were mounted one above the other with a vertical spacing of 5 mm between adjacent coils. Alternate coils were rotated 90° with respect to each other to reduce coupling. The whole system was surrounded by a container filled with FC-43. For the 2-coil system at 500 MHz, the microcoils were constructed as described above, one on a 75 μ m i.d. 360 μ m o.d. capillary ($V_{obs} = 5$ nL) and the other on a 200 μ m i.d. 360 μ m o.d. capillary ($V_{obs} = 31$ nL). The coils were then mounted on double-sided printed circuit boards. The capillaries were oriented at the magic angle with respect to the B_0 field, and the two boards attached back-to-back with copper shielding between the boards. The matching networks were designed to maximize the distance between the elements of the two circuits, with the microcoils separated by 5 mm transversely with respect to the B_0 field. The NMR probe modules disclosed here differ

from such earlier devices in having multiple detectors, each having a detection site, i.e., as described above, void in the capillary microchannel to receive a test sample, and having an NMR microchannel aligned therewith.

In the first paragraph on page 26, please amend the specification follows:

The microchannels and associated NMR microcoils can be formed in a module, preferably a multi-layer substrate, such as a laminated multi-layer substrate, e.g., a selectively welded multi-layer substrate as disclosed in copending United States patent application Serial No. 60/239,010 filed on October 6, 2000, the entire disclosure of which is incorporated herein by reference for all purposes. Microlithographic microcoils can be employed in such laminate substrates, such as those disclosed in the above-mentioned US patent 5,684,401, the entire disclosure of which is incorporated herein by reference for all purposes. Alternatively, or in addition, one or more of the multiple NMR detector sites formed in the probe can be formed in a finger or peninsula-type extension of the substrate, and the microcoil can be formed as a separate 3-dimensional structure fitted over such substrate projection. It will be within the ability of those skilled in the art, that is, those skilled in this area of technology, given the benefit of this disclosure, to employ alternative suitable fabrication techniques for production of the multi-microcoil NMR detection probes disclosed here.

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